Planning Pregnancy for Infected, Exposed, or Possibly Exposed Individuals

In September 2016, the ASRM issued a Zika guidance for providers that addressed the care of non-pregnant patients desiring pregnancy. This document, now updated, is based on new information, including the recent MMWR Vol. 67, August 7, 2018 issued by the CDC, “Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Men with Possible Zika Virus Exposure – United States, August 2018.” In particular, this revised ASRM document addresses those individuals and couples undergoing assisted reproductive technologies (ART) who are potentially imminently pregnant because of the high overall success rate of this infertility treatment, compared to other treatments and natural conception. These couples therefore should be considered to be in the periconceptional period and for them, this can be defined prospectively, whereas for those who conceive naturally, this period is defined retrospectively. Unlike patients attempting pregnancy on their own, achieving a pregnancy by an intervention such as ART is voluntary, and the active role of providers falls under the guiding principle of medicine of “do no harm.” This document was developed to specifically address couples who may be needing ART and/or the use of gametes and embryos.

1. **Reproductive health care providers should perform preconception counseling that includes a discussion of diagnostic challenges and unmitigated risks.** Currently available data are accumulating with time but continue to be incomplete.
   - In areas of active Zika virus transmission, health care providers should discuss strategies to prevent congenital Zika virus infection and unintended pregnancy, including use of the most effective contraceptive methods. In addition, as Zika has been shown to be transmitted sexually, patients should be counseled that correct and consistent use of condoms reduces the risk for sexually transmitted infections.
   - Discussions about pregnancy timing should be individualized and should include information about the signs and symptoms of Zika virus disease and the potential adverse outcomes associated with Zika virus infection in pregnancy, even in those asymptomatic infected women. Preliminary data from the CDC reported that Zika virus-associated birth defects occurred in 10% of pregnancies with laboratory-confirmed Zika virus infection, and in 15% of pregnancies where Zika virus infection occurred during the first trimester.
   - The CDC reported that of 1450 babies born in the US Territories after confirmed or possible Zika virus infection during pregnancy, one in seven evaluated had a neurodevelopmental condition that could possibly be related to Zika virus infection. Most children did not have all the recommended evaluations; thus, additional anomalies might not have been identified.
   - Currently, although there are limited data, there is no evidence that Zika virus will cause congenital infection in pregnancies initiated after the resolution of maternal Zika viremia.
   - Male and female partners who become infected should avoid intimate sexual contact or use condoms during the time that they delay attempts of pregnancy. Transmission through vaginal and anal sex has been demonstrated. Animal studies suggest that an enhanced viral dissemination during sexual transmission while pregnant may pose a greater risk than the subcutaneous transmission from a mosquito bite. Data on transmission through oral sex and the sharing of sex toys are still lacking.
   - If the male or female partner of a pregnant woman becomes infected or tests positive for Zika virus, he or she should avoid intimate sexual contact as described above or use condoms for the duration of the pregnancy.

2. **Infertility treatment centers caring for patients at risk of infection during the course of treatment or subsequent pregnancy should develop strategies to mitigate the risk of viral transmission to the patient and the fetus.** Standard infection control precautions should protect health care workers.
Strategies should incorporate sufficient counseling about the challenges of interpreting test results, even from direct viral RNA testing, the Zika virus nucleic acid test (NAT). For instance, Zika RNA may persist for longer durations in bodily fluids, such as semen, and for shorter periods of time in serum. Whether to be tested or not must take into consideration the declining prevalence of Zika, the possibility of false-positive and false-negative results, and the chance of becoming infected with Zika after testing, and should involve a shared patient-provider decision-making model.

Any patient with possible exposure to Zika virus who proceeds with attempting pregnancy after negative viral testing should be counseled about the possible presence of virus with a negative test (i.e., a false-negative result), the risks of subsequent infection in at-risk women, the possible viral effects on the fetus (e.g., congenital brain abnormalities), and testing during pregnancy as per national or regional guidance.

3. **Men who have confirmed Zika virus disease should wait at least 3 months after onset of illness to attempt reproduction.** For women with confirmed Zika disease, the CDC recommends waiting 8 weeks while the WHO suggests a more conservative approach of waiting 6 months to attempt pregnancy. The temporal relationship between the presence of viral RNA and infectivity is not known definitively and, thus, the absolute duration of time to wait before attempting pregnancy is unknown. In one study, semen samples were analyzed over time in one hundred eighty-four Zika virus positive men. Although the virus persisted in one sample up to 281 days, only 7% had detectable ZIKV RNA after 90 days (mean time for clearance was 54 days). Infectious Zika virus was detected by plaque assay in only 3 of 19 samples within 30 days, and in none of the samples collected past 30 days". Additionally, data available are increasingly supportive of an 8-week wait only for women as viral persistence in blood is short for them and they do not appear to have any other immunologically protected sites.

- The decision to wait 8 weeks (CDC) vs. 6 months (WHO) for the woman and 3 vs. 6 months for men with Zika virus disease should be made using a shared patient-provider decision-making model taking into account any new available data and such variables as age of the female patient and other infertility factors with documentation of the conversation and decision.

4. **Symptomatic women and men attempting pregnancy through ART with possible Zika virus exposure should have testing** that includes the Zika virus nucleic acid test (NAT) to rule out active Zika infection, and serologic testing, as outlined in section #8 below, to identify Zika immunity, before proceeding on with infertility treatment. One must remember that men, however, may harbor Zika virus in semen after NAT testing in blood becomes negative. If testing is performed, attempting pregnancy should be considered only if NAT is negative. Otherwise, the couple should delay attempts at pregnancy using the same guidance of known infected individuals. Couples should understand that testing may be costly.

5. **Asymptomatic women and men undergoing ART with possible exposure to Zika virus or who have traveled to a zone of possible Zika exposure should wait 8 weeks for women and 3 months for men.** Alternatively, they should consider testing for Zika infection, the decision again being made using a shared patient-provider decision-making model. If testing is opted, it should begin with NAT and be followed by serology testing as outlined in section #8 below at or beyond 15 days from exposure by which time Zika IgM would be positive if infection occurred with the exposure. If testing is performed, attempting pregnancy should not be considered if NAT is positive. If immunity to Zika is inferred by either prior positive NAT or serology testing, future NAT testing is not needed for subsequent ART treatments.

6. **Women and men who reside in areas of active Zika virus transmission should talk with their health care providers about attempting reproduction.**
   - Patients desiring pregnancy should be counseled about the risks of infection during pregnancy and methods to avoid infection.
   - Ideally, patients living in areas of active Zika transmission would delay attempts at pregnancy until the risk of infection during pregnancy is minimal. Here is a link to the latest CDC map of such areas:
Asymptomatic women and men with ongoing Zika virus exposure who decide to undergo ART should be offered Zika virus testing (NAT), to avoid proceeding with a NAT-positive patient, and possibly serology testing to potentially identify Zika immune patients who can proceed with treatments avoiding subsequent NAT testing so long as 3 months has passed from best calculated infection for men and 8 weeks for women. If opted during a planned fresh cycle, this testing should be timed as close to the retrieval as is practical and at a time that will allow the review of results before the retrieval. Similarly, if opted in a planned thaw transfer cycle, the testing should be performed as close to the time of transfer as is practical and at a time that will allow the review of results before the transfer. As stated above, patients tested should understand the occurrence of false-negative and false-positive results and be reminded that infection can occur at any time after the testing.

For males or females with a positive NAT result, treatment of infertility should be halted immediately. It should be deferred until 1) a subsequent NAT is negative on both the male and female and 2) at least 3 months have passed in the male and 8 weeks to 6 months have passed in the female from the time of the last positive result.

7. Additional strategies may be considered for asymptomatic couples residing in a Zika area of active transmission undergoing ART treatment.

- For males or females without testing or with a negative NAT test result who are concerned that they have false negative testing or may become infected after testing, consideration can be given for gamete or embryo cryopreservation and quarantine until: 1) a subsequent NAT re-test is negative on both the male and female and 2) at least 8 weeks have passed from the time of the gamete collection.
- For males, not previously infected with the Zika virus who are planning travel to an area of active virus transmission, consideration can be given to semen cryopreservation before travel. Ideally, they should be tested for Zika virus RNA at the time of semen collection and within 1 week after return.
- Both of these scenarios are predicated on the belief that the semen samples are free of Zika. There is no evidence that cryopreservation of sperm kills the virus and recent evidence demonstrates that Zika may persist in washed semen samples.\(^1\)

Zika Testing Limitations

8. Testing for Zika can present challenges because of the variable availability of tests, the information provided by tests, and the interpretation of results. Testing is not universally available for use in those individuals for whom testing is recommended and the cost is not universally covered by insurance. Reproductive health care providers should identify the tests that are available in their community, the limitations and interpretation of the results of these tests, which patients will be allowed testing by these testing facilities, and whether testing is covered by insurance. Ideally this information would be obtained before patients who are infected or at-risk for infection present for care.

- A generalized testing paradigm for a symptomatic exposed individual might begin with NAT. If NAT is positive a Zika diagnosis may be given realizing that false positive results may occur. If NAT is negative in high prevalence areas, IgM testing is indicated. IgM results that are positive, equivocal, presumptive positive or possible, should be followed up with plaque reduction neutralization tests (PRNT) for dengue and Zika as PRNT can identify the causative virus and may uncover false-positive IgM. PRNT might not differentiate between cross-reacting antibodies in individuals previously infected or vaccinated with another flavivirus and anti-Zika virus antibodies. As such, in low prevalence areas, the IgM false-positive rate may increase because of exposure to these other flavivirus infections or vaccines.

9. Although Zika virus can be present in semen and cervical and vaginal secretions and sexual transmission of the virus has occurred between partners of the same and opposite sex, **testing of semen and cervical and vaginal fluids is not recommended** until methods for detecting Zika virus in semen or bodily fluids other than serum or urine are validated.

10. Evidence suggests that a positive test for Zika viral RNA in serum is likely associated with the presence of virus in semen or other bodily fluids. A negative serum test result by NAT would not necessarily preclude the presence of the
virus in semen or other bodily fluids. Patients should be provided counseling regarding interpretation of the test results.

**SUMMARY TABLE. CDC recommendations for preconception counseling and prevention of sexual transmission of Zika virus among persons with possible Zika virus exposure — United States, August 2018**

<table>
<thead>
<tr>
<th>Exposure scenario</th>
<th>Recommendations (update status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only the male partner travels to an area with risk for Zika</td>
<td>The couple should use condoms or abstain from sex for at least 3 months after the male partner’s symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). (Updated recommendation)</td>
</tr>
<tr>
<td>virus transmission and couple planning to conceive</td>
<td></td>
</tr>
<tr>
<td>Only the female partner travels to an area with risk for Zika</td>
<td>The couple should use condoms or abstain from sex for at least 2 months after the female partner’s symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). (No change in recommendation)</td>
</tr>
<tr>
<td>virus transmission and couple planning to conceive</td>
<td></td>
</tr>
<tr>
<td>Both partners travel to an area with risk for Zika</td>
<td>The couple should use condoms or abstain from sex for at least 3 months from the male partner’s symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). (Updated recommendation)</td>
</tr>
<tr>
<td>virus transmission and couple planning to conceive</td>
<td></td>
</tr>
<tr>
<td>One or both partners have ongoing exposure (i.e., live in or frequently travel to an area with risk for Zika virus transmission) and couple planning to conceive</td>
<td>The couple should talk with their health care provider about their plans for pregnancy, their risk for Zika virus infection, the possible health effects of Zika virus infection on a baby, and ways to protect themselves from Zika. If either partner develops symptoms of Zika virus infection or tests positive for Zika virus infection, the couple should follow the suggested timeframes listed above before trying to conceive. (No change in recommendation)</td>
</tr>
<tr>
<td>Men with possible Zika virus exposure whose partner is pregnant</td>
<td>The couple should use condoms or abstain from sex for the duration of the pregnancy. (No change in recommendation)</td>
</tr>
</tbody>
</table>


**Fertility Treatments Using Autologous or Donated Gametes**

11. **Fertility treatment for sexually intimate couples using their own gametes and embryos should follow the timing recommendations for persons attempting reproduction.**

12. **The Food and Drug Administration (FDA) guidance remains unchanged in the May 2018 update, stating that living donors of human cells, tissues, and cellular and tissue-based products (including sperm, oocytes, and embryos) should be considered ineligible for donation if they have any of the following risk factors:**

   - medical diagnosis of Zika virus infection in the past 6 months;
   - residence in or travel to an area with an increased risk of Zika virus transmission within the past 6 months;
   - or sex within the past 6 months with a person who has either of the risk factors listed in items 1 or 2, above.

13. **Directed (or known) donors must undergo the same evaluation and eligibility determination as anonymous donors.**

14. **Fertility treatment using a gestational carrier should follow timing recommendations for gestational carriers as for persons attempting reproduction.**
15. When using donated embryos, consideration should be given as to the potential exposure of the embryos to Zika virus, particularly if the embryos were frozen at a time of active Zika transmission and before screening processes were in effect.

16. It is tempting to assume that the use of techniques for sperm preparation that have been shown to be effective for minimizing the risk of HIV transmission should be similarly effective for minimizing risk of Zika virus transmission. However, these procedures have not yet been demonstrated to be effective in preventing transmission of the Zika virus nor has cryopreservation been demonstrated to destroy the Zika virus. In a recent publication, motile sperm obtained after sperm washing were found to have Zika virus RNA in 3 of 14 patients at day 7 and, by day 20, 4 of 15 patients.1

17. Data involving Zika, its transmission and infectivity, and its adverse effects on fetuses and adults is changing daily. Guidance based on current knowledge is iterative as our understanding of this virus rapidly changes. Any guidance published today may not be accurate for counseling and treatment of individuals tomorrow. Refer to the CDC Zika website for the most updated information. https://www.cdc.gov/zika/

18. It is suggested that until more data are available about asymptomatic males and females potentially exposed to Zika, practitioners providing treatment that involves use of gametes in potentially infected individuals develop language to be added to their consent forms that conveys this gap in knowledge to these individuals.

References


Duggal NK, McDonald EM, Ritter JM, Brault AC. Sexual transmission of Zika virus enhances in utero transmission in a mouse model. Sci Rep 2018;8:4510.


This report was developed under the direction of the Zika Virus Guidance Task Force* of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Executive Committee of the American Society for Reproductive Medicine has approved this report.

* Zika Virus Guidance Task Force members: G. David Ball PhD, Nabal Bracero MD, Maria Bustillo MD, Owen Davis MD, Susan Gitlin, PhD, Avner Hershlag MD, Jennifer Kawwass MD, Samantha Pfeifer MD, Richard Reindollar MD, James Segars MD, Sean Tipton MA, Bradley Van Voorhis MD, Michael Vernon PhD

Rev. August 2018